

## REMARKS

Reconsideration of this application, as amended, is respectfully requested.

Claims 44-48, 73, and 75-82 are pending. Claims 44-45 and 48 are amended to further clarify the scope of the claimed invention. Claims 81 and 82 are added to incorporate the amended subject matter of claim 45. The amendments are fully supported by the specification, for example, on page 11, as originally filed. Thus, the amendments do not constitute new matter.

### A. Claim Objections

The Examiner objected to claims 44-45, 75 and 77 for the following informalities. Applicants thank the Examiner for pointing out the informalities and suggesting amendments. The claims have been amended as suggested and thus the objections have now become moot.

In paragraph 13, Claim 44 is objected to for reciting “indicative for presence of.”

Applicants have amended claim 44 to recite “indicative of presence of” as suggested by the Examiner.

In paragraph 14, the Examiner requested clarification of the relationship of “a specific analyte” to the “plurality of analytes derived from one pathogen” in claim 44(d).

Claim 44(d) has been amended to recite “the analyte of the plurality of analytes,” and thus obviating the objection.

In paragraph 15, Claim 45 is objected to as confusing for reciting two ands in the Markush-type group. Additionally, in paragraph 18 the Examiner requested in the first instance a recitation of the full terms of the abbreviations HIV, HBV, and HCV in claims 45, 75, and 77.

Claim 45 has been amended to recite “human immunodeficiency virus I (HIV I)-antibodies, human immunodeficiency virus II (HIV II) -antibodies, and HIV antigens.” In addition, new claims 81 and 82 recite “human hepatitis B virus (HBV)” and “human hepatitis C virus (HCV)”, respectively.

In paragraph 16, inconsistency is asserted as to the recitation of a “signal generating group” in claim 44 and “signal-generating group” in claim 48.

Claim 48 has been amended to recite a “signal generating group” to ensure consistency between claims.

In paragraph 17, the Examiner requested clarification of the relationship of various analytes to each other as recited in claim 44. Specifically, Applicants are requested to clarify

whether the analyte-specific receptors are specific for the analytes to be detected, and whether the different analytes refers to different analytes among the plurality of analytes to be detected.

Applicants has amended claim 44(a) for clarification to recite “each analyte-specific receptor is specific to an analyte of the plurality of analytes in the sample, and wherein the first receptor and the second receptor bind to different analytes of the plurality of analytes in the sample.” Thus, the objection is now moot.

**B. Rejections under 35 U.S.C. §112, First Paragraph, Written Description**

Claims 44-48, 73, 75-80 stand rejected for allegedly failing to comply with the written description requirement under 35 U.S.C. § 112, first paragraph. Specifically, the Examiner asserted that one skilled in the art would recognize that for a given analyte the threshold for a positive assay would differ depending on how the COI is calculated. The Examiner further asserted that because claims are not limited in the manner by which a COI is calculated, the incorporation of the limitation “wherein a COI larger than 1 for one test area is indicative for presence of a specific analyte in the sample” out of the context of the disclosure represents new matter. Additionally, the Examiner asserted that the specific COI disclosed on page 30 of the specification was in the context of a specific assay, i.e., assay for HIV-1 p24 antigen.

Sufficient written description is required under 35 U.S.C. §112, first paragraph to inform a skilled artisan that Applicants were in possession of the claimed invention at the time of filing; however, what is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986).

Applicants traverse the rejection but have nevertheless amended the claims. Claim 44 as amended is directed to a method for detection of a pathogen by detecting a plurality of analytes in a sample, the plurality of analytes derived from infection by the pathogen, wherein a COI larger than 1 for either one of the first and second test areas is indicative of presence of the analyte that binds to the first or second test area and is indicative of presence of the pathogen in the sample. Thus, a single pathogen is determined via different markers by determining the respective markers in individual test areas, whereby a positive result as evidence by a COI larger than 1 for one of a plurality of markers indicates the presence of the pathogen in the sample.

It is commonly understood, and further taught in the specification, that a COI larger than 1 in a bridge detection format indicates a positive test result. This is supported even by the references cited in the Action as evidence of state of the art, for example, Yuki et al. (Hepatology, 1995, 22:402-6) and Chan et al. (US 5,120,662). It is commonly understood that when the processed sample signal is larger than a predetermined cut-off (thus,  $\text{COI} > 1$ ), the test result is positive.

The Examiner asserted that there is no generic disclosure that any calculated COI greater than 1 would indicate a positive result. As support for the assertion, the Examiner pointed to the example on pages 28-30 of the specification where, in a back titration detection format, a COI greater than 1 indicates negative results. Applicants respectfully contend that the assertion is misplaced.

Example 4 on page 28 clearly indicates that in a sandwich bridge format, a COI larger than 1 indicates positive results. The results were confirmed by *an alternative back titration format*, in which a COI larger than 1 would indicate negative results. One of skill in the art would understand that this exception is seen and expected only when the assay principle is reversed in the back titration format.

Claim 44 as amended is directed to a detection method wherein each third receptor is *specific for one or more analytes of the plurality of analytes* bound to the first and second test areas. As explained on page 15 of the specification, in a back titration format, however, a labeled third receptor is added to compete with the binding of the analyte to the first or second receptor immobilized on the solid phase. Thus, the third receptor in the back titration testing format is specific for the first or second receptor immobilized on the solid phase, and NOT to the analytes in the sample. Thus, the back titration testing format is not encompassed by the claims. And one of skill in the art would understand that claim 44 recites a detection method wherein a test area-specific COI larger than 1 indicates positive results.

The specification provides a generic disclosure that is further evidenced by the detection of various analytes in a bridge detection format, including p24 antigen, anti-p24 antibody, gp41 peptide 1 antigen, gp41 peptide 2 antigen, anti-gp41 peptide 1 antibody, anti-gp 41 peptide 2 antibody, and anti-RT antibody. See Examples 1-4. In all the cases, the disclosure has demonstrated that a COI larger than 1 indicates a positive result. Thus, the claimed method has general applicability and is not limited to the detection of p24 antigen only.

Further, the Examiner's assertion that for a given analyte, the threshold for a positive assay would differ depending on how the COI is calculated is also incorrect. The Examiner

referred to the equation of claim 78 as an example and asserted that if the cut-off is increased by a factor of 3 in the event that  $n$  is increased by a factor of 3, a COI great than 3 (rather than greater than 1) would signify a positive assay. Applicants wish to point out that a cut-off index (COI) is different from a cut-off threshold, or a cut-off: a cut-off may vary depending on the background levels for a given analyte; however, COI is a fixed standardization, irrespective of the adjustment of cut-offs. A COI that is larger than 1 simply indicates that the sample signal is larger than the cut-off, thus signifying a positive test result. When the cut-off is adjusted by a factor of 3 as in the Examiner's hypothetical, it is the *sample signal*, not the COI, that would have to similarly increase by a factor of 3 to be considered a positive test result. Thus, one of skill in the art would understand that the COI that signifies a positive test result (usually larger than 1) is a constantly held standard irrespective of the adjustment of the cut-off for a given analyte.

Thus, the claimed invention is fully supported by the disclosure. One of skill in the art would recognize that Applicants had possession of the claimed invention commensurate with the scope of the claims at the time of filing. Accordingly, Applicants respectfully request reconsideration and withdrawal of the written description rejection.

**C. Rejections under 35 U.S.C. §112, Second Paragraph**

The Examiner rejected Claims 44-48, 73, 75-80 for alleged being indefinite under 35 U.S.C. § 112, second paragraph. Specific rejections are listed below.

In paragraph 22, the Examiner rejected claim 44 because the recitation of the term “derived from” is allegedly unclear. Specifically, the Examiner asserted that the term “derived from” is undefined, and, although both HIV antigens and antibodies specific for the antigens are disclosed, it is unclear by what process(es) the analytes would be “derived.”

Applicants submit that amended claim 44 reciting “the plurality of analytes derived from infection by the pathogen” is definite under 35 U.S.C. § 112, second paragraph. It would have been clear the metes and bounds of the claim because the process (infection) from which the plurality of analytes was derived is clear.

In paragraph 23, Claim 44 stands rejected because the recitation of “the test area” in part (b) allegedly lacks sufficient antecedent basis.

Claim 44(b) has been amended to recite: “the first and second test areas,” thus obviating the rejection.

In paragraph 24, Claim 44(c) stands rejected because the recitation of “the first and second test areas” allegedly lacks sufficient antecedent basis as there is no prior mention that the signal generating group is bound to the first and second test areas.

Claim 44(b) as amended recites “...allow binding of the one or more third receptors to the plurality of analytes bound to the first and second test areas”, wherein each third receptor is directly or indirectly labeled with a signal generating group. Thus, there is sufficient antecedent basis for a signal generating group bound to the first and second test areas and hence the rejection is now moot.

In paragraph 25, Claim 44 is rejected because the recitation of “the analytes bound to the test area” in part (b) allegedly lacks sufficient antecedent basis. Further, the reference to “the analytes” is purportedly unclear in light of the recitation of “a plurality of analytes derived from one pathogen,” “analyte-specific receptors,” and “different analytes.” The Examiner further rejected the claim because it is unclear how each different analyte would bind to the test area since each test area has a receptor specific for a different analyte.

The references to analytes in claim 44 have been amended to a “plurality of analytes.” The recitation in amended claim 44(b) of “...to allow binding of the plurality of analytes to the first and second test areas...” provides adequate antecedent basis for “the plurality of analytes bound to the test areas.” Additionally, although each test area is designed for a specific analyte among the plurality of analytes, it is clear that “the plurality of analytes” as a whole could bind to the first and the second test areas. Thus, the claim is clear and the rejection has become moot.

In paragraph 26, Claim 44 stand rejected because it is unclear how the COI larger than 1 is calculated and because the COI is variable.

Applicants traverse the rejection. As stated above in pages 7-8 of the instant response, a COI larger than 1 is a universally understood concept and commonly adopted standardization for signaling a positive test result. In contrast to the Examiner’s assertion, while the cut-off thresholds may vary, the level of a *cut-off index* (COI) that signifies a positive result *remains constant*; a COI larger than 1 indicates positive detection results.

One of the inventive concepts of the instant application is the use of a test area-specific COI, while the calculation of each COI is not limited to any particular equations. As stated above and

further evidenced by the references cited in the Action as state of the art, COI is a well understood concept. Equations for calculating COI are also well known to one of ordinary skill in the art. Thus, the metes and bounds of the claim are clear.

In paragraph 27, Claim 44 is also rejected for omitting essential step of detecting the plurality of analytes. The Examiner requested a correlation step be included to describe how the results of the method accomplish the objective as recited in the preamble.

Claim 44 as amended is directed to a method for detection of a pathogen by detecting a plurality of analytes in a sample. The claim comprises steps of detecting at least two analytes of the plurality of analytes in the sample and the presence of at least one analyte of the plurality of analytes is indicative of the presence of the pathogen in the sample. Thus, the claim as amended describes how the objective recited in the preamble is accomplished.

In paragraph 28, The Examiner asserted that claim 44 omits an essential structural cooperative relationship that the third receptors are specific for one of the analytes to be detected.

Amended claim 44(b) now recites “wherein each third receptor is specific for one or more analytes of the plurality of analytes bound to the first and second test areas.” Applicants submit that each third receptor need not be specific for only one of the plurality of analytes but could be specific for one type of the plurality of analytes. For instance, the analytes binding to the first and second test areas are anti-HIV p24 and anti-HIV RT antibodies, respectively. One of skill in the art would understand that the third receptor could be a reagent that recognizes human antibodies, and thus, “specific for one or more analytes of the plurality of analytes bound to the first and second test areas.” The indefinite rejection has therefore been rendered moot.

In paragraph 29, Claim 48 stands rejected because claim 44 already recites that the detection reagent “comprises at least one third receptor” that “is directly or indirectly labeled with a signal generating group.”

Applicants submit that amendment to claim 48 has rendered the rejection moot.

**D. Rejections under 35 U.S.C. § 102**

The Examiner rejected Claim 44-45, 47-48, 73, and 76-79 under 35 U.S.C. § 102(a) as being unpatentable by Karl et al. (WO 99/05525, or US 6,815,217) (“the ‘217 patent”). Specifically, the Examiner asserted that the ‘217 patent teaches assaying a plurality of analytes derived from a single pathogen detected by analyte-specific receptors immobilized on discrete test areas on a solid support. With regard to claims 78-79, the Examiner asserted that the ‘217 patent teaches a similar formula with different terminology for calculating COI. Examiner further asserted that the ‘217 patent teaches a negative control field that is a control field without solid phase receptor. Applicants respectfully traverse the rejection.

As a threshold matter, the Federal Circuit has stated that for prior art to anticipate under section 102, every element of the claimed invention must be identically disclosed in a single reference. *Corning Glass Works v. Sumitomo Electric*, 9 U.S.P.Q.2d 1962, 1965 (Fed. Cir. 1989). The exclusion of a claimed element, no matter how insubstantial or obvious, from a reference is enough to negate anticipation. *Connell v. Sears, Roebuck & Co.*, 220 U.S.P.Q 193, 198 (Fed. Cir. 1983).

Further, it is clear from the decisions of the Court of Appeals for the Federal Circuit that in order to anticipate a claimed invention, a prior art reference must enable one of ordinary skill in the art to make the invention without undue experimentation. *Finisar Corp. v. DirectTV Group, Inc.*, 523 F.3d 1323, 1336 (Fed. Cir. 2008).

The ‘217 patent does not anticipate the claimed invention because, *inter alia*, the ‘217 patent does not teach a detection method for a pathogen by detecting a plurality of analytes derived from the pathogen in a sample, comprising a step of calculating a test area-specific cut-off index (COI) for *each analyte of the plurality of analytes* based on a test area-specific background detected from a signal generated by any signal generating group non-specifically bound to the inert solid phase. Throughout the ‘217 patent, however, only one analyte, HBsAg, was detected, and only one COI, the COI for HBsAg, was calculated. The Examiner referred to the Tables of the ‘217 patent for the purported teachings of a test area-specific COI. However, the ‘217 patent does not and cannot teach a test area-specific COI for each analyte *in the context of a plurality of analytes* because the ‘217 patent measures only ONE analyte. Simply put, the ‘217 patent does not teach, and more importantly, does not enable one of skill in the art to detect a pathogen by detecting a plurality of analytes derived from the pathogen, wherein the presence of each analyte is determined by a test area-specific cut-off index for *each analyte of the plurality of analytes*.

Although Figure 1 of the '217 patent may have suggested the possibility of simultaneous measuring HIV antibodies, HBV antigen, and HCV antibodies, the suggestion amounts to nothing more than an invitation to experiment. The '217 patent does not constitute an enabling disclosure of the current invention. It can hardly be said that the '217 patent teaches one skilled in the art simultaneous measuring of a plurality of analytes derived from one pathogen, wherein the COI for each analyte of the plurality of analytes is separately determined based on a test area-specific background detected from a signal generated by any signal generating group non-specifically bound to the inert solid phase, and wherein a COI larger than 1 for at least one of the plurality of analytes indicates the presence of the pathogen. Thus, the '217 patent does not teach every element of claim 44.

Additionally, Claims 78-79 are directed to a method of detection of a plurality of analytes wherein the test area-specific COI is calculated by the formula:  $COI = \frac{\text{signal}_{\text{sample}} - \text{background}_{\text{sample}}}{n} \times \text{background}_{\text{negative control}}$ , wherein n ranges between 2 and 100. The '217 patent, on the other hand, relates to a formula  $COI = [\text{Signal}(\text{test field}) - \text{signal}(\text{negative control field})]/3 \times \text{signal}(\text{negative control})$ . The Examiner's assertion that the two equations are different only in the terminology is misplaced. For example, "background<sub>sample</sub>" of the instant claim is not the same as "signal (negative control field)" of the '217 patent. In the '217 patent, the negative control area refers to a designated common control area, the signal of which is compared with those of all test spots (see Figure 3 and claim 1). In the instant invention, however, the background<sub>sample</sub> is the sample specific background measured for example from the inert solid phase between test spots without a specific coating, and NOT from a designated common control area on the solid phase (see page 11 of the specification). Thus, the '217 patent does not teach a sample specific background and does not teach every element of claims 78-79.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 USC § 102(a) of claim 44 and dependent claims 45, 47-48, 73, and 76-79 over the '217 patent.

#### **E. Rejections under 35 U.S.C. §103(a)**

The Examiner raised several rejections under 35 U.S.C. § 103(a) of claims 44-48, 73, 75-80 as being obvious. Specific rejections are listed below.

In paragraph 33, Claim 46 is rejected under 35 USC § 103(a) as obvious over the '217 patent. Specifically, the Examiner asserted that the '217 patent teaches that the test areas most preferably have a diameter of 0.01 mm to 2 mm, which largely overlaps the range of 0.01 mm to 1 mm recited in claim 46. The Examiner asserted that a *prima facie* case of obviousness exists because one of skill in the art would have arrived at the claimed range by routine optimization.

A claimed invention is unpatentable if the differences between it and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a); *see Graham v. John Deere Co.*, 383 U.S. 1, 14 (1966). The ultimate determination of whether an invention is or is not obvious is based on underlying factual inquiries including: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the pertinent art; and (4) evaluating evidence of secondary considerations. *See Graham*, 383 U.S. at 17-18.

The Supreme Court emphasizes that the key of supporting any rejection under 35 U.S.C. §103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. *KSR Int'l Co. v. Teleflex Inc.*, 127 U.S. 1727, 1741 (2007). The Court, quoting *In re Kahn*, stated that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441, F.3d 977, 988 (Fed. Cir. 2006).

Applicants submit that claim 46 is not obvious over the '217 patent because the claim depends on non-obvious claim 44. Claim 44 is directed to a method for detection of a pathogen by detecting a plurality of analytes derived from the pathogen in a sample comprising the step of calculating a test area-specific cut-off index (COI) on each test area based on a test area-specific background detected from a signal generated by any signal generating group non-specifically bound to the inert solid phase, wherein a COI larger than 1 for either of the first and second test area is indicative of presence of an analyte of the plurality of analytes that binds to the first or second test area, which is indicative of the presence of the pathogen in the sample.

The '217 patent, on the other hand, merely relates to detection of one analyte in a sample. Thus, the '217 patent does not teach detecting a plurality of analytes and certainly does not teach calculating a test area-specific COI for each analyte. Most importantly, the '217 patent does not recognize and appreciate the advantage of a test area-specific COI for each analyte in that positive detection of a specific analyte is not overshadowed by the high background of other

analytes. Applicants respectfully submit that the skilled worker cannot glean from the '217 patent to understand the benefit of a test area-specific COI. Thus, claim 46 would not have been obvious over the '217 patent.

In paragraph 34, Claim 80 stands rejected under 35 USC § 103(a) as obvious over the '217 patent in view of purported general knowledge in the art as evidenced by the following seven references: Ohkawa et al. (J. Hepatol. 1994, 21:509-14) ("Ohkawa"), Ohnishi et al. (Gastroentero Jpn. 1991, Suppl. 3:212-5) ("Ohnishi"), Hyman et al. (US 5,384,240) ("Hyman"), Chan et al. (US 5,120,662) ("Chan"), Lesniewski et al. (US 6,596,476) ("Lesniewski"), Kiyosawa et al. (Gastroenterol. Jpn. 1986, 21:601-7) ("Kiyosawa"), and Yuki et al. (Hepatology, 1995, 22:402-6) ("Yuki"). Claim 80 depends on claim 79, which ultimately depends on claim 44.

Specifically, the Examiner asserted that although the '217 patent does not teach a COI equation using an  $n$  value of 2, when taken together with the general knowledge in the art, it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention by optimizing the equations disclosed in the '217 patent.

In essence, Ohkawa and Ohnishi relate to a cut-off index calculated by simply dividing the sample value with a cut-off. Neither Ohkawa nor Ohnishi, however, teaches or suggests detection of a plurality of analytes, much less the calculation of a test area-specific COI for each analyte of the plurality of analytes as a determination of the presence of the analyte. Ohkawa and Ohnishi do not teach or suggest a COI equation with an adjustable  $n$  value that could be determined separately for each analyte of a plurality of analytes. Further, in a common ELISA test as described in Ohkawa, it is not possible to simultaneously measure a sample-specific background.

Hyman and Chan were cited for the proposition that the concept of a cut-off index equal or greater than 1 signifies a positive test result was known in the art. Yuki purportedly teaches assessing samples as positive when the samples have a cut-off index  $>1$ , wherein the cut-off is taken as 4 times the mean negative control sample signal. Lesniewski describes that a general cut-off may be calculated as about 2.1 to 8 times the negative control mean absorbance value. Further, the Kiyosawa reference discloses a cut-off index calculated by the equation: cut-off index = (net count of sample / mean of net count of negative control)  $\times 1/2.1$ .

The Examiner asserted that the references collectively disclose that a cut-off index can be obtained by dividing the assay signal with a cut-off, which can be established by reference to a

negative control multiplied by various numerical values. However, none of the seven references cited as the general knowledge in the art teaches a method of simultaneously detecting *a plurality of analytes*, wherein the COI for each analyte of the plurality of analytes is individually calculated based on a test area-specific background detected from a signal generated by any signal generating group non-specifically bound to the inert solid phase, and if necessary, separately adjusted with different numerical value of n. Further, none of the cited references recognizes and appreciates the advantages of a test area-specific COI for each analyte in that positive result of a specific analyte is not overshadowed by the high background of other analytes. Additionally, none of the seven references describes a COI equation remotely resembling, or rendering obvious, the claimed equation:  $COI = \frac{\text{signal}_{\text{sample}} - \text{background}_{\text{sample}}}{n \times \text{background}_{\text{negative control}}}$ .

The Examiner asserted that one of skill in the art would recognize that the equation for calculating a COI in the '217 patent, purportedly similar to the claimed equation, represented a variation on the known cut-off index calculations known in the art. In fact, the '217 formula is fundamentally a very different formula, and the concept of eliminating false positivity applied by the '217 patent is fundamentally a very different concept, from those of the seven cited art. The seven cited references, particularly Lesniewski, merely relate to modulating detection specificity by adjusting the *denominator* of the equation of cut-off index. In contrast, the '217 patent discloses adjusting the *numerator* of the equation by subtracting the signal of the negative control field from the signal of the test area, while the calculation of the denominator remains unchanged. In addition, the '217 patent teaches that any non-specificity resulted from the interfering human anti-mouse antibody (HAMA) present in the sample can be reduced by further subtracting the HAMA signal from the sample signal. See Example 2 of the '217 patent. Thus, one of ordinary skill in the art would not have considered the '217 formula simply a variation of the cut-off index known in the art. Accordingly, one of ordinary skill in the art would not have been motivated to combine the '217 patent with the other seven references.

The claimed equation for calculating a COI is further removed from the '217 formula. As stated above, the " $\text{background}_{\text{sample}}$ " of the instant claim is not the same as "signal (negative control field)" of the '217 patent. In the '217 patent, the negative control area refers to a designated common control area, the signal of which is compared with those of all test spots (see Figure 3 and claim 1). In the instant invention, however, the  $\text{background}_{\text{sample}}$  is the sample specific background measured for example from the inert solid phase between test spots without

a specific coating, and NOT from a designated common control area on the solid phase (see page 11 of the specification).

Further, the '217 patent teaches adjusting the numerator of the formula to achieve higher specificity; the '217 patent, however, does not teach that it is necessary or desirable to adjust both the numerator AND the denominator of a COI formula for improving the specificity of detection. Similarly, none of the cited seven references teaches that it is necessary or desirable to adjust both the denominator AND the numerator of a COI equation for improving the specificity of detection. It would not have been obvious to one of ordinary skill in the art based on the '217 patent to further manipulate the denominator by multiplying the negative control signal with a value different from 3, given that the numerator of the formula has already been adjusted. Accordingly, it would not have been obvious to one of skill in the art to measure a test-area specific COI for each analyte of a plurality of analytes by subtracting from the sample signal a sample-specific background signal in the numerator as well as adjusting the levels of the denominator by multiplying the negative control signal with a value of 2.

In paragraph 35, Claims 44-45, 47-48, 73, and 75-77 are rejected under 35 USC § 103(a) as obvious over O'Connor (US 5,627,026) ("O'Connor").

Specifically, the Examiner asserted that O'Connor discloses assessment of simultaneous detection of antigens and antibodies associated with the same viral infection. The Examiner further asserted that O'Connor teaches that a sample signal that is three times greater in absorbance intensity than the negative control is regarded as positive.

The Examiner acknowledged that O'Connor relates the sample signal to the negative control value only in the discussion of ELISA test of one FIV analyte, and not a plurality of analytes. Nevertheless, the Examiner asserted that it would have been obvious to one of skill in the art to construct positive and negative controls for both antigen and antibody analytes to be detected. The Examiner further asserted that it would have been obvious to calculate a COI for antibody as well as for antigen to determine whether the sample was in fact positive for the presence of each of these analytes.

Applicants respectfully traverse the rejections. O'Connor only theoretically describes the simultaneous determination of an HIV antigen and HIV antibody, but never shows or enables one of ordinary skill how it is done. Contrary to the O'Connor method, the present invention is far more sensitive because it uses a test area-specific COI wherein a COI larger than 1 for at least one test area indicates the presence of the pathogen.

Moreover, the Examiner's assertion that O'Connor also determines a test area-specific COI is incorrect. O'Connor discloses the threshold of a sample value relating to a control mean, which is not the disclosure of an individual COI calculated for each test field. See Col. 8, lines 30 to Col. 9 line 25 of O'Connor. O'Connor simply compares the sample signal with the signal of the designated common negative control well. One of skill in the art would not have easily derived a test area-specific COI from the disclosure of O'Connor. Further, O'Connor describes measuring extinction in a liquid; a spatially resolved measurement of an extinction in solution, however, is not possible. Therefore, O'Connor does not and cannot teach a test area-specific COI that is calculated based on a test area-specific background detected from a signal generated by any signal generating group non-specifically bound to the inert solid phase.

O'Connor is devoid of any teachings of a "test area-specific COI" because O'Connor does not recognize the advantages of a "test area-specific COI." One of ordinary skill in the art would not have been motivated to modify O'Connor to arrive at the claimed methods, in which specificity can be improved without affecting the high sensitivity. The superiority of the claimed invention is achieved by the use of a test area-specific cut-off index that is not recognized by O'Connor. Thus, Applicants respectfully submit that claim 44, and dependent claims 45, 48, 73, and 75-77 are not obvious over O'Connor.

In paragraph 36, Claim 46 stand rejected under 35 USC § 103(a) as obvious over O'Connor in view of Ekins (US 5,837,551)("Ekins"). Specifically, the Examiner asserted that O'Connor teaches test areas on non-porous solid supports, and Ekins teaches microspots preferably having an area of less than 0.1 square mm, e.g., a diameter of 0.08 mm.

Claim 46, which depends on claim 44 with the additional limitation that the test area has a diameter of 0.01 to 1 mm is not obvious over O'Connor in view of Ekins. As discussed above, O'Connor does not teach or suggest, *inter alia*, the concept of and the ways to calculate a "test area-specific COI." O'Connor simply compares the sample signal with the signal of the negative control spot. The problem with a common cut-off limit for all parameters is that the cut-off limit is determined and constrained by the unspecific binding of the worst component. Applicants recognized the problem and provided a solution of using a test area-specific COI where the specificity for a detection method for a plurality of analytes is improved without affecting the overall sensitivity of the assay. O'Connor does not recognize the problems encountered when detecting a plurality of analytes and does not appreciate the solution of using a "test area-specific COI." Ekins merely relates to the size of the test areas and certainly does not cure the defects.

One of ordinary skill in the art would not have been motivated to modify O'Connor to arrive at the invention an improved method of detecting a plurality of analytes achieved by a test area-specific cut-off index. Thus, Applicants respectfully submit that claim 46 is not obvious over O'Connor in view of Ekins.

In paragraph 37, Claims 78-80 are rejected under 35 USC § 103(a) as obvious over O'Connor in view of Carpenter ("Enzyme-linked immunoassays" In: Manual of Clinical Laboratory Immunology, Noel R. Rose et al. (Eds), ASM Press, Washington, DC (1997) 5<sup>th</sup> Ed., pp. 20-29)("Carpenter"), and further in view of the seven references cited in paragraph 34: Ohkawa, Ohnishi, Hyman, Chan, Lesniewski, Kiyosawa, and Yuki.

Specifically, the Examiner asserted that while O'Connor does not teach first subtracting "background sample" from the numerator in the claimed equation, Carpenter teaches that when detecting colorimetric substrates by spectrophotometry in ELISA assays, OD measurements can be blanked on a well containing either substrate, substrate-Ab conjugate alone, or a negative serum in an uncoated well. Thus, the Examiner asserted that subtracting a background measurement for the sample to produce a corrected signal is tantamount to blank the spectrophotometer as described in Carpenter, and the claimed invention would have been obvious to one of skill in the art.

With regard to the multiplier  $n$  in the denominator of the equation, the Examiner asserted that O'Connor effectively teaches multiplying the negative control value by a factor of 3, and determining whether the signal  $\text{sample} / \text{background negative control}$  is greater than 1. Additionally, citing the seven references Ohkawa, Ohnishi, Hyman, Chan, Lesniewski, kiyosawa, and Yuki as support, the Examiner asserted that a cut-off index calculated by dividing the sample signal with the signal of negative control multiplied by a numerical value is known in the art. The Examiner thus concluded that it would have been obvious to one of ordinary skill in the art to modify the teachings of O'Connor and Carpenter to manipulate an already blanked sample signal value by dividing it with the negative control signal multiplied by a adjustable numerical value.

Applicants respectfully submit that when making an obviousness rejection, the Examiner must consider the claimed invention "as a whole." MPEP 2141.02. The invention, as a whole, is directed to a method of detecting a plurality of analytes, wherein the presence of an analyte of the plurality of analytes is determined based on the value of a test area-specific COI for *each analyte* of the plurality of analytes. None of the cited art teaches or suggests a test area-specific cut-off index for each analyte of the plurality of analytes. The problem with a common cut-off

limit for all parameters is that the cut-off limit is determined and constrained by the unspecific binding of the worst component. Applicants recognized the problem and provided a solution of using a test area-specific COI where the specificity for a detection method for a plurality of analytes is improved without affecting the overall sensitivity of the assay. The test area-specific COI for each analyte is calculated by both subtracting sample-specific background from the sample signal, and adjusting the modified sample signal by dividing the signal with the negative control signal multiplied by a numerical value, wherein the numerical value is adjusted in case false positivity for a given analyte of the plurality of analytes is detected.

Carpenter merely relates to detecting a target analyte in ELISA assays in each test. Carpenter, however, does not teach or suggest simultaneously detecting a plurality of analytes in a sample. Further, Carpenter discloses “blanking” the sample signal in a designated common negative control well in the 96-well assay; however, Carpenter does not teach or suggest “blanking” the sample signals with respect to each and every analyte of the plurality of analytes in a sample.

Additionally, the background<sub>sample</sub> of the instant invention is the sample specific background measured for example from the inert solid phase between test spots without a specific coating. The explicit claim element is not taught by O'Connor, Carpenter or any of the cited seven references. A spatially resolved measurement in a liquid assay such as ELISA is not possible and thus not obvious in view of O'Connor and Carpenter.

Additionally, neither O'Connor nor Carpenter teaches or suggests the need or desirability for further modifying the processed sample signal with the negative control signal multiplied by an *adjustable* value. Similarly, none of Ohkawa, Ohnishi, Hyman, Chan, Lesniewski, kiyosawa, and Yuki references teaches or suggests assessing a sample signal by anything other than comparing the sample signal with the negative control signal or with the negative control signal multiplied by a fixed numerical value.

Applicants respectfully submit that the Examiner has not established as to why, in the absence of the teachings in the cited art, one of skill in the art would have been motivated to combine different ways of correcting the sample signals, with a reasonable expectation that the signal is not over-corrected and that the positive result is not overlooked. Further, the Examiner has not explained as to why the missing claim element not taught by the combination of references is obvious to one of ordinary skill in the art.

Based on the above, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a).

**F. Double Patenting**

Claims 44-48, 73, and 75-77 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-34 of U.S. Patent No. 6,815,217 (“the ‘217 patent”) in view of Schonbrunner (GB 2 313 666A).

Applicants respectfully traverse the rejections but nevertheless file herewith a terminal disclaimer with regard to the co-owned U.S. Patent No. 6,815,217. Applicants submit that the terminal disclaimer has rendered the double patenting rejection moot.

**G. Conclusion**

Reconsideration of this application is respectfully requested and a favorable determination is earnestly solicited. The Examiner is invited to contact the Applicants’ undersigned representative at (312) 913-2126 if the Examiner believes that this would be helpful in expediting prosecution of this application.

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Respectfully,  
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